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(*Reprinted from Nature, Vol.* 187, *No.* 4739, *pp.* 804–805, *August* 27, 1960)

Mechanisms of Meiotic Non-disjunction in Man

It is now well known that there is an abnormal chromosome number in mongolism in chromatin-positive Klinefelter's syndrome, and in chromatin-negative Turner's syndrome. It is also known that mongolism is associated with increased maternal age, and there is some evidence that a similar association exists in chromatin-positive Klinefelter's syndrome[1,2] and in chromatin-negative Turner's syndrome[1]. In cases of chromatin-positive Klinefelter's syndrome previously studied the available data (Table 1) provide supporting evidence that there is an association with, among other possibilities, increased maternal age. Fifty-four cases were classified with respect to position in the sibship. Four were in the centre of the sibship and of the remaining 50 cases, 17 were in the first half and 33 in the second half. This is significantly different from the expected 25 to 25 distribution.

It is generally agreed that meiotic non-disjunction is the most probable cause of these conditions. Further information about the number and origin of *X* chromosomes can be obtained from colour-blindness studies[2–5]. A colour-blind chromatin-positive case of Klinefelter's syndrome with colour-normal parents could be due to a defect of oogenesis. This was pointed out independently by Stewart[3] and Stern[6]. Stern considers that available data on chromatin-positive Klinefelter's syndrome suggest an abnormality of the first meiotic division but they are, in fact, equally consistent with a defect of the second meiotic division. The expected frequency of colour-blindness following a second meiotic abnormality

Table 1. Position of Patient in Sibship

Number in sibship	1	2	3	4	5	6	7	8	9	10	11	12	13	
1	3													3
2	3	10												13
3	0	1	8											9
4	1	2	0	2										5
5	0	1	0	1	5									7
6	1	0	1	1	0	1								4
7	0	0	0	0	0	0	2							2
8	0	0	0	1	0	0	0	1						2
9	1	0	0	0	0	0	0	1	0					2
10	0	0	1	0	0	0	0	0	1	3				5
11	0	0	0	0	0	0	0	0	0	0	1			1
12	0	0	0	0	0	0	0	0	0	0	0	0		0
13	0	1	0	0	0	0	0	0	0	0	0	0	0	1
	9	15	10	5	5	1	2	2	1	3	1	0	0	54

which he quotes (8 per cent) is correct for a locus close to the centromere but he does not consider the expected frequency for a locus sufficiently far from the centromere to give random segregation. The frequency of females homozygous for colour-blindness is 0·5 per cent. All XX eggs from such individuals will be homozygous recessive for colour-blindness. The frequency of females heterozygous for colour-blindness is 15 per cent and with random segregation one-sixth of their secondary oocytes will carry the gene for colour-blindness on both chromatids. Non-disjunction at the second meiotic division gives exceptional XX eggs and 2·5 per cent of these will be homozygous recessive (one-sixth $\times$ 15 per cent). The expected frequency of colour-blindness in exceptional individuals due to a second meiotic abnormality is therefore 3 per cent (2·5 per cent from heterozygous mothers and 0·5 per cent from homozygous mothers). Thus the expected limits of colour-blindness incidence in exceptional individuals following an abnormality of the second meiotic division of oogenesis are 3–8 per cent. Collection of further data may provide information about the position of the colour-blindness locus relative to the centromere, about the relative frequency of non-disjunction in oogenesis and spermatogenesis and about the state of meiosis at which non-disjunction occurs[5].

There is good evidence that some cases of chromatin-negative Turner's syndrome are due to a defect of spermatogenesis and that some cases of chromatin-positive Klinefelter's syndrome are due to a defect of oogenesis; and the opposite situations probably occur[5]. A defect of oogenesis may be assumed if a colour-normal case of chromatin-negative Turner's syndrome is found with a colour-blind mother and a colour-normal father, and a defect of spermatogenesis would be indicated by a colour-normal case of chromatin-positive Klinefelter's syndrome with a colour-blind mother and a colour-normal father[5]. Defects of spermatogenesis in the chromosomal intersexes may be related to the unequal size of the X and Y chromosomes with consequent failure of pairing leading to non-disjunction during meiosis. In oogenesis all chromosomes are paired, but a similar causal mechanism might operate for a chromosomal aberration such as inversion could lead to failure of pairing and non-disjunction. A chromosomal aberration of this sort might be inherited or it might be caused by environmental influences. A possible clue to the mechanism is provided in the reports that mongolism is associated with increased maternal age but not with increased paternal age[1], and that there is

little increase in the number of female germ cells after birth[7]. Environmental influences, including temperature, hormones and those such as radiation which cause genetic change, may predispose to defects of oogenesis but not to defects of spermatogenesis if old women have old eggs but old men have young sperm.

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IT is useful at this stage of human cytogenetics to keep in mind the whole spectrum of possibilities of chromosomal behaviour. In this sense Dr. Stewart's emphasis on the possibility of non-disjunction during the second meiotic division is valuable. His discussion rests on the assumption that non-disjunction is preceded by crossing-over between homologous chromosomes. In my discussion of second division non-disjunction I had specified absence of crossing-over (and, thus, made no assumption as to closeness of the locus for colour blindness to the kinetochore). According to Dr. Stewart's scheme it would follow that genes distantly located would less often become homozygous than proximal genes. This is the opposite to what is well established in *Drosophila*, although it cannot be excluded, of course, that human chromosomes may behave differently. In *Drosophila* the more frequent homozygosis for distal than proximal genes signifies that non-disjunction preceded by crossing-over occurs during the first meiotic division.

Apart from the question whether non-disjunction occurs during the first or second meiotic division, Ford's suggestion that it may also occur in early cleavage cannot be dismissed[1]. This suggestion accounts for homozygosis of the locus for colour-blindness by mitotic non-disjunction without reference to crossing-over or of gene location.

I wish to add two minor points in reference to my earlier communication: (1) The statement about a

'maximum' of recessive homozygosis of 16·7 per cent was in error; instead this frequency follows from random assortment. (2) The choice of 0·5 per cent as the incidence of colour-blind women was made for the sake of a round number; 0·45 or 0·4 per cent are more accurate values.

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Printed in Great Britain by Fisher, Knight & Co., Ltd., St. Albans